

## REMARKS/ARGUMENTS

Claims 55, 63, 64, 65, 75, 80, 81, and 90-96 have been amended in order to place them in condition for allowance, or in better form for consideration on appeal. Claims 58 and 78 have been cancelled without prejudice or disclaimer. Claims 55-57, 59-77 and 79-96 remain pending upon entry of this amendment.

Claims 58 and 78 were cancelled because amendment of the claims from which they depended rendered them redundant.

Claims 55, 64 and 75 have been amended to recite that the human matrix metalloproteinase is "constitutively enzymatically active." Support for this amendment can be found throughout the specification and in particular on page 6 lines 8-10, page 8 lines 14-15, page 12 lines 5-8 and lines 13-14, page 26 lines 11-13, and in Example 1.

Claims 55, 63-65, 75, 80, and 81 have been amended to recite that the promoter is "joint-specific." Support for this amendment can be found throughout the specification and in particular on page 6 lines 15-17 and lines 18-20, page 15 line 19 - page 16 line 9, page 36 line 21 - page 37 line 1, and in Examples 4 and 5.

Claims 59 and 79 have been amended to change the claim from which they depend because the claims from which they originally depended (claims 58 and 78, respectively) have been cancelled.



### **Information Disclosure Statement**

The Examiner has stated that the Information Disclosure Statement (IDS) filed February 28, 2001 is improper because the citations are allegedly incomplete. Specifically, the Examiner has requested that the US Patents list the date, name, class and subclass, and that information for the foreign patents and publications be completed. The Examiner has also indicated that citation number 4 of the PTO Form 1449 filed with the IDS on February 28, 2001, DE 19501032 A1, has not been considered because a translation has not been provided.

This Amendment is accompanied by a PTO form SB-08A in which each of the citations that had been listed in the February 28, 2001 PTO Form 1449 are listed in complete form. As requested by the Examiner, all information has been completed for these citations. The Form SB-08A submitted herewith does not list any references not previously made of record in the February 28, 2001 PTO Form 1449.

This Amendment is also accompanied by an English abstract of citation number 4, DE 19501032 A1. It is believed that Applicants have therefore met the "concise explanation" requirement of 37 § C.F.R. 1.98. In accordance with MPEP Sections 609 and 707.05(b), it is requested that DE 19501032 A1 be given thorough consideration and that it be cited of record in the prosecution history of the present application by initialing Form SB-08A next to the document.

It is respectfully noted that each of the references cited in the Form SB-08A submitted herewith was cited in an IDS and considered by the Examiner in the parent application

U.S.S.N. 08/994,689. MPEP § 609 I A (2) requires that the Examiner consider all information which had been considered by the Office in a parent application. Thus, this Form SB-08A and the English abstract of DE 19501032 A1 are being submitted herewith solely in order to assure that these citations will be printed on the face of the patent that issues from the present application.

It is believed that the Applicants' duty to disclose information material to patentability under 37 § C.F.R. 1.56 has been met. Applicants respectfully request entry of the accompanying PTO Form SB-08 and English abstract of DE 19501032 A1 and withdrawal of the objection to the Information Disclosure Statement.

**Rejections under 35 U.S.C. § 112, first paragraph- written description**

Claims 55-96 have been rejected for alleged failure to fulfill the written description requirement because of the phrase "chondrocyte tissue-specific promoter." In this rejection, the Examiner states that specification and the art do not teach that the Type II collagen promoter is expressed only in chondrocytes.

The phrase "chondrocyte tissue-specific promoter" has been deleted from the claims and claims 55, 63-65, 75, 80, and 81 have been amended to recite that the promoter is "joint-specific." Joint-specific promoters are well-described and enabled by the instant application.

There is literal support in the specification for "joint-specific promoter." (See page 6 lines 15-17 and lines 18-20, page 15 line 19 - page 16 line 9, page 36 line 21 - page 37 line 1,

and Examples 4 and 5 of the specification). The specification clearly teaches that spatial control of MDE expression is achieved by the use of transcriptional promoters that direct transcription selectively in joint tissues. (See specification at page 15, lines 19-20). Such joint specific expression is clearly defined as that which produces expression in non-joint tissue of less than 10%, and preferably not at all. (*Ibid.* at lines 20-23). One source of such joint specific promoter sequences includes those derived from the collagen type II promoter. (See specification at page 16, lines 1-2). Finally, the specification teaches that such joint-specific promoter sequences may comprise one or more copies of particular sequences or sub-sequences, and that these may be in direct or inverted orientation relative to each other or the sequence being regulated. (*Ibid.* at lines 2-6).

The concept of joint-specific promoters was well-known in the art at the time of invention. As set forth in the Second Neuhold Declaration (paragraph 7; a copy of the Second Neuhold Declaration and its accompanying Exhibits (Tabs 1-9), which were originally filed in the parent case U.S.S.N. 08/994,689 on August 31, 2000, was filed as Exhibit 5 with the April 30, 2002 Amendment and Response in the instant application), the specific promoter employed to achieve tissue specific expression does not make any difference, as one of ordinary skill in the art would readily appreciate. A number of issued patents that cover transgenic animals establish tissue-specific expression is sufficiently enabled for expression of a transgene, because the actual tissue specific promoter is usually of no moment. See for example U.S. Patent Nos. 5,625,124 (claim 1: "gut epithelial cell specific promoter"); 5,880,327 (claim 1:



enzymatically active. Accordingly, it is believed that this rejection has been obviated and Applicants respectfully request its withdrawal.

The Examiner has rejected claims 55-64, 66-79 and 81-96 for alleged lack of enablement because of the phrase "chondrocyte-specific promoter." The present amendment has replaced this phrase with the phrase "joint-specific promoter" in these claims.

When making this rejection, the Examiner cites Niemann 1997 (Transg. Res. Vol. 7, p. 73-75) as evidence that an assertion made by Dr. Neuhold in her Second Declaration is incorrect, namely Dr. Neuhold's assertion that the promoter used to achieve tissue specific expression does not make a difference. Specifically, the Examiner alleges that Niemann taught that transgenic pigs made with different promoters regulating growth hormone expression caused different phenotypes (one deleterious, one compatible).

Applicants respectfully note that the Examiner has mistakenly based his rejection on an erroneous reading of the reference. The passage pointed to by the Examiner in Niemann (p. 73 Col. 2, ¶ 2, line 12 to p. 74 Col. 1, line 4) describes the deleterious outcome of a non-tissue specific promoter as compared to the compatible outcome of a tissue-specific promoter. Thus, this reference clearly supports the assertion made in the Second Neuhold Declaration and demonstrates that a tissue-specific promoter is important for the desired outcome. Given the importance of tissue-specific expression of the transgene to the invention, as supported by Niemann, and the ease with which one of ordinary skill can substitute one promoter for another, it is well within the level of skill to use any joint-specific promoter in this invention,

whether known or yet to be discovered. In other words, as disclosed in the application, tissue-specific expression is very important, but the exact tissue-specific promoter used to achieve it matters very little. Since any such claim would be to the transgenic animal as claimed, the term "joint-specific promoter" does not unfairly "preempt the future before it has arrived" as the Examiner suggests (see page 3 of the Final Office Action).

In view of these arguments and those made in the preceding section (under 112, written description), Applicants assert that a transgenic non-human mammal comprising a "joint-specific promoter" is enabled and described by the instant application. Accordingly, Applicants respectfully request withdrawal of this rejection.

The Examiner has rejected claims 55-63, 67-71, 75-91, and 93-96 for alleged lack of enablement because of the phrase "transgenic non-human mammal." When making this rejection, the Examiner cited references previously of record, namely Mullins (1990), Hammen (1990), Mullins (1989), Taurog (1988), Mullins (1996), Mullins (1993), Ebert (1988), and Wall (1996), and two references previously not of record (Mullins 1993, Hypertension, Vol. 22, p. 630-633: herein "Mullins 1993"; and Cameron 1997, Mol. Biol. Vol. 7, p. 253-265: herein "Cameron 1997").

The Examiner cites Cameron 1997 for teaching that transgene expression is unpredictable because of the effects of genetic background and insertion site on transgene expression. The Examiner then concludes that "since mice and rats having [sic] increased



genetic diversity, the unpredictability of whether the phenotype obtained in mice would occur in rats is increased.” (see page 15 of the Final Office Action).

Applicants respectfully disagree and traverse this rejection. Nothing in Cameron 1997 supports the Examiner’s assertion that increased genetic diversity (i.e., different species) is related to the unpredictability of transgene expression. Rather, the reference discusses the effects of the placement of the transgene with respect to the overall chromatin structure on transgene expression. Nothing in Cameron correlates diversity of chromatin structure with species-specificity. As described by Cameron, the effect of placement of the transgene with respect to overall chromatin structure is an issue relevant even within species and is not species dependent (see p. 256 col. 2 lines 3-9 of Cameron which describes that such effects are seen with transgenic mice (not between species) made with the same construct). Thus, Cameron supports Applicants’ assertion that at the time of the present invention, it was routine for one skilled in the art to screen, whether the screening be done within or between species, for transgenic animals that work, i.e., in which transgene insertion occurs at an accessible location in the chromosome.

Cameron does not correlate genetic diversity or species diversity with unpredictability of transgene expression. Rather, Cameron discloses that *all* transgene expression depends on random insertion of the transgene in a productive integration site, both within and between species, and that it is routine for one skilled in the art to test and make transgenic animals to find one with the desired phenotype.



that integration of a transgene into a different species of animal results in divergent phenotypes. Mullins 1993 is simply a review article that summarizes references that were already of record (specifically Mullins 1990 and Hammer 1990 (see p. 631 Col. 1 end of ¶ 1 of Mullins 1993)). These references also show that, as with many experimental biological processes, creating a desired transgenic animal requires multiple trials, with screening and selection processes to select the successes. The Examiner has failed to establish any reason why the transgenic animal differs from the other biological arts, such as that discussed in *In re Wands*, in this respect.

For the reasons advanced in the Second Neuhold Declaration, the specification enables claims to non-human transgenic mammals. In particular, ". . . contrary to the examiner's assertions, as of 1996 creation of transgenic mammals required no more than ordinary technical efforts – indeed, technical efforts with shortcomings that are readily overcome" (Neuhold Declaration, paragraph 9). All of these techniques are set forth in the specification at pages 22-26. Moreover, this clear assertion by one of ordinary skill in the art outweighs the Examiner's misunderstanding of the cited transgenic animal references.

In short, the Examiner's grounds for rejection are in error given the advanced state of the art, including general recognition of enablement of creation of transgenic animals (irrespective of whether or not such efforts are cost effective), widespread knowledge of regulatable expression systems, the understanding in the art of tissue-specific expression, and the number of well known extracellular matrix degrading enzymes from which to choose. The

present invention is broadly enabled, and the Examiner has not met his burden of challenging enablement with reasonable evidence. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph is in error and should be withdrawn.

**Rejections under 35 U.S.C. § 112, second paragraph-indefiniteness**

Claim 90 has been rejected for alleged indefiniteness because the scope of “non-human mammal” and “transgenic mammal” on lines 2 and 4, respectively, is not commensurate. Line 2 has been amended to recite “non-human transgenic mammal.” Thus, this rejection has been obviated and Applicants respectfully request its withdrawal.

Claims 90-96 have been rejected for indefiniteness because the Examiner contends that steps (a) and (b) do not make it clear when the compound is administered to the mammal relative to administering the regulatory compound, obtaining MMP expression and Type II collagen degradation. Step (a) of claims 90-96 have been amended to recite that the composition is administered to a transgenic mammal “in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal.” Accordingly, this rejection has been obviated and Applicants respectfully request its withdrawal.

The Examiner has also rejected claims 90-96 because step (b) of these claims is allegedly confusing and because there is allegedly no antecedent basis for the phrase “the extent of...” because the listed phenotypes are not required in step (a) or in the parent claims.

Claims 90-96 have been amended to provide antecedent basis for the phrase “the extent of phenotypic change” in step (b) of the claims by specifying in the preamble and in step (a) of the claims that phenotypic changes occur (e.g. loss of proteoglycan, cleavage of Type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof) in the transgenic animal. Accordingly, these rejections have been obviated and Applicants respectfully request their withdrawal.

The Examiner has also rejected claims 90-96 for alleged indefiniteness because the metes and bounds of the control animal are unclear. The Examiner has also inquired as to whether the control animal is transgenic.

Claims 90-96 have been amended to recite that the control animal is “transgenic.” In addition, these claims have been amended to recite that the control transgenic mammal is one “in which the composition was not administered but expression of the metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered.” Page 20 line 23 - page 21 line 2 of specification also clearly describes the metes and bounds of a control animal:

Control animals comprise age- and sex-matched transgenic animals that are maintained under an identical regimen (i.e. express the transgenes) but which do not receive the composition.

Thus, it is believed that this rejection has been obviated and Applicants respectfully request its withdrawal.

Claims 90-96 were rejected for alleged indefiniteness because the Examiner found it unclear how to determine the “difference” in a phenotypic “change” and whether the test requires comparing the development of the phenotypes listed in both test and control mammals, comparing a characteristic over a period of time, or comparing a characteristic at a specific time in the test and control animals. Lastly, the Examiner has rejected claims 90-96 for alleged indefiniteness because he believes the claim states that any “change” indicates the composition may counteract osteoarthritis.

Claims 90-96 have been amended to clarify that any less extensive development in the nature or extent of the phenotypic change, or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal indicates the potential of the composition to counteract the phenotypic change. Thus, the claims are clear on how to determine the difference in a phenotypic change or changes and the claims indicate that the difference in a phenotypic change indicates the potential of the composition to counteract the phenotypic change. The utility of the invention lies in that this model system permits identification of lead compounds that may be useful to treat osteoarthritis. Thus, it is believed that these rejections have been obviated and Applicants respectfully request their withdrawal.

## Conclusion

The amendments made herein have been made in order to place the claims in condition for allowance or in better form for consideration on appeal. In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

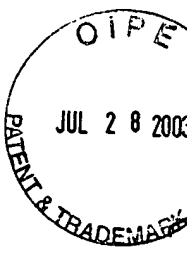
If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

**Dated: July 28, 2003**

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Appl. No.: 09/717,450

Applicant: Lisa A. Neuhold and Loran Marie G.A.U.: 1632  
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Filed: November 20, 2000 Examiner: Michael C. Wilson

Title Transgenic Animal Model for Degenerative Diseases of Cartilage

Docket No.: 0630/1D5321US1

Mail Stop AF  
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**COURTESY COPY OF PENDING CLAIMS**

Sir:

Claims 1-54 (Cancelled)

Claim 55 (Currently Amended): A transgenic non-human mammal whose genome  
comprises:

Appl. No. 09/717,450  
Courtesy Copy of Pending Claims. Dated July 28, 2003  
Accompanying Reply to Office Action of April 9, 2003  
{M:\0630\1d532us1\00032195.DOC }

Page 1



(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the regulatable promoter in the absence of a repressor-activator fusion polypeptide-binding compound and does not bind to the regulatable promoter in the presence of the compound, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a joint-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the mammal until adulthood, and wherein the metalloproteinase is capable of being expressed in the mammal during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mammal.

Claim 56 (Previously Added): The transgenic mammal of claim 55, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

Claim 57 (Previously Added): The transgenic mammal of claim 56, wherein the matrix metalloproteinase is MMP-13.

Claim 58 (Cancelled)

Claim 59 (Currently Amended): The transgenic mammal of claim 57, wherein the MMP-13 comprises the sequence of SEQ ID NO: 1 or SEQ ID NO: 21.

Claim 60 (Previously Added): The transgenic mammal of claim 55, wherein the repressor-activator fusion polypeptide is a chimeric tetracycline repressor-VP16 transcription activator polypeptide and the regulatable promoter is a Tn10 sequence linked to a portion of the CMV IE promoter.

Claim 61 (Previously Added): The transgenic mammal of claim 60, wherein the regulatable promoter comprises the sequence of SEQ ID NO: 2.

Claim 62 (Previously Added): The transgenic mammal of claim 55, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of Type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 63 (Currently Amended): The transgenic mammal of claim 55, wherein the joint-specific promoter is a Type II collagen promoter.

Claim 64 (Currently Amended): A transgenic rat whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a tetracycline-regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the tetracycline regulatable promoter in the absence of tetracycline or a tetracycline analog and does not bind to the regulatable promoter in the presence of tetracycline or tetracycline analog, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a joint-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the rat until adulthood, and wherein the metalloproteinase is capable of being expressed in the rat during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the rat.

Claim 65 (Currently Amended): The transgenic rat of claim 64, wherein the matrix metalloproteinase is constitutively enzymatically active MMP-13, the tetracycline-regulatable promoter is tet07, the repressor-activator fusion polypeptide is tTA, and the joint-specific promoter is a Type II collagen promoter.

Claim 66 (Previously Added): The transgenic rat of claim 64, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.



such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic mammal.

Claim 70 (Previously Added): The method according to claim 69, wherein the tetracycline analog is doxycycline.

Claim 71 (Previously Added): The method according to claim 69, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 72 (Previously Added): A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises

(a) maintaining the transgenic rat of claim 64 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating expression of the matrix metalloproteinase by withholding the tetracycline or tetracycline analog from the rat after the rat has reached adulthood, such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic rat.

Claim 73 (Previously Added): The method according to claim 72, wherein the tetracycline analog is doxycycline.



Claim 76 (Previously Added): The transgenic mammal of claim 75, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

Claim 77 (Previously Added): The transgenic mammal of claim 76, wherein the matrix metalloproteinase is MMP-13.

Claim 78 (Cancelled)

Claim 79 (Currently Amended): The transgenic mammal of claim 77, wherein the MMP-13 comprises the sequence of SEQ ID NO: 1 or SEQ ID NO: 21.

Claim 80 (Currently Amended): The transgenic mammal of claim 75, wherein the joint-specific promoter is a Type II collagen promoter.

Claim 81 (Currently Amended): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to an ecdysone receptor ligand-binding domain, and wherein the transgenic mammal further comprises a nucleotide sequence encoding a retinoid X receptor (RXR), which nucleotide sequence encoding RXR is operatively linked to a joint-specific promoter.

Claim 82 (Previously Added): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a progesterone receptor ligand-binding domain.

Claim 83 (Previously Added): The transgenic mammal of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a steroid binding domain.

Claim 84 (Previously Added): The transgenic mammal of claim 75, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 85 (Previously Added): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 75 in the absence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering the compound to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 86 (Previously Added): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:



(a) maintaining the transgenic mammal of claim 81 in the absence of ecdysone, an ecdysone analog, or dexamethasone until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering ecdysone, an ecdysone analog, or dexamethasone to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 87 (Previously Added): A method for producing degradation of Type II collagen in the joints of a transgenic non-human mammal, which method comprises:

(a) maintaining the transgenic mammal of claim 82 in the absence of mifepristone (RU 486) until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic mammal by administering mifepristone (RU 486) to the mammal after the mammal has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the mammal.

Claim 88 (Previously Added): The method according to claim 86, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 89 (Previously Added): The method according to claim 87, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

Claim 90 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

- (a) administering the composition to the transgenic mammal of claim 55 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal; and
- (b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the

metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered, wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the phenotypic change.

Claim 91 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

- (a) administering the composition to the transgenic mammal of claim 60 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal; and
- (b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the

metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered, wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the phenotypic change.

Claim 92 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

- (a) administering the composition to the transgenic rat of claim 64 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic rat; and
- (b) comparing the extent of the phenotypic change in the rat to which the composition was administered with that of a control transgenic rat in which the composition was not administered but expression of the metalloproteinase was

activated at the same age as it was activated in the animal in which the composition was administered,

wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the rat that has been administered the composition relative to the control rat, indicates the potential of the composition to counteract the phenotypic change.

Claim 93 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

- (a) administering the composition to the transgenic mammal of claim 75 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal; and
- (b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the



metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered, wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the phenotypic change.

Claim 95 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

- (a) administering the composition to the transgenic mammal of claim 82 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal; and
- (b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the

metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered, wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the phenotypic change.

Claim 96 (Currently Amended): A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a non-human transgenic mammal, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TC<sup>A</sup> degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

- (a) administering the composition to the transgenic mammal of claim 83 in which a phenotypic change has been produced by activation of expression of the metalloproteinase during adulthood of the transgenic mammal; and
- (b) comparing the extent of the phenotypic change in the mammal to which the composition was administered with that of a control transgenic mammal in which the composition was not administered but expression of the



metalloproteinase was activated at the same age as it was activated in the animal in which the composition was administered, wherein any less extensive development in the nature or extent of the phenotypic change or any increased length of time required for the phenotypic change to develop in the mammal that has been administered the composition relative to the control mammal, indicates the potential of the composition to counteract the phenotypic change.